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Additional inventors are being named on the 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

LOW OSMOLAR X-RAY CONTRAST MEDIA FORMULATIONS

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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☐ Application Data Sheet. See 37 CFR 1.76

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Respectfully submitted,

SIGNATURE Jeffrey S. Boone

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Docket Number 1667.P US

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Number 2 of 2

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LOW OSMOLAR X-RAY CONTRAST MEDIA FORMULATIONS

FIELD OF THE INVENTION

The present invention generally relates to contrast media formulations and, more particularly, to nonionic x-ray contrast media formulations, radiological compositions containing such agents and methods for x-ray visualization utilizing such compositions.

BACKGROUND OF THE INVENTION

The search for ideal contrast media for X-ray radiodiagnostic studies has extended over many decades. Bismuth subnitrate was the first radiocontrast agent used for visualization of the alimentary tract. Later, barium sulfate, a safer agent, was introduced. Barium sulfate has remained the most widely used radiographic agent for the alimentary tract (W.H. Strain, International Encyclopedia of Pharmacology and Therapeutics, Section 76, Vol. 1, Radiocontrast Agents, Chapter 1, Historical Development of Radiocontrast Agents, 1971, Pergamon Press). The inorganic, insoluble oral agents like bismuth subnitrate and barium sulfate serve as valuable tools for gastrointestinal radiodiagnosis.

Unlike gastrointestinal radiodiagnosis, urographic and angiographic X-ray procedures, require intravascular administration of a safe, water-soluble, radiopaque contrast medium. Since the introduction of the water-soluble ionic triiodobenzoic acid derivatives, such as diatrizoic acid and iothalamic acid, in the early 1960's, radiographic visualization of the vascular system has become the most important application of X-ray contrast media. These X-ray procedures are valuable in the diagnosis and evaluation of a variety of diseases that involve or cause alterations in normal vascular anatomy or physiology.

Preferred intravascular X-ray contrast agents possess a combination of desirable properties. Such properties include the following to various degrees: (1) maximum x-ray opacity; (2) biological safety; (3) high water solubility; (4) chemical stability; (5) low osmolality; and (6) low viscosity. In particular, studies

have shown that high osmolality can be correlated with undesirable physiologic adverse reactions to x-ray contrast media, *e.g.*, nausea, vomiting, heat and pain.

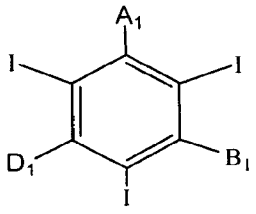
A significant advancement in the area of triiodobenzene X-ray contrast media has been the development of nonionic triiodobenzoic acid derivatives such as iopamidol, iohexol and ioversol. In general, aqueous solutions of these non-ionic agents have less osmolality than previous agents and hence, provide greater patient comfort when injected. Adverse reactions, especially in the sensation of pain, warmth, and hemodynamic effects are greatly reduced as compared to the ionic triiodobenzoic acid derivatives.

Further reduction of osmolality of X-ray contrast media resulted from the introduction of nonionic dimeric agents such as iotrolan and iodixanol. These agents, as compared to the nonionic monomeric agents, provide even greater patient comfort by reducing nausea and vomiting upon intravenous injection and by causing much less pain upon peripheral arterial injection. The viscosity of such nonionic dimeric agent-based formulations, however, is generally greater than for the corresponding monomeric analogs.

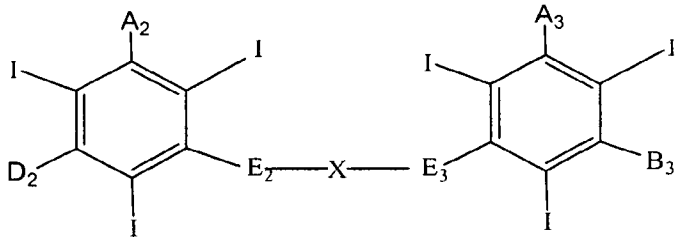
SUMMARY OF THE INVENTION

Among the various aspects of the present invention may be noted the provision of nonionic contrast agents, radiological compositions and methods for x-ray visualization; and the provision of such agents with improved osmolality and viscosity which are substantially non-toxic.

Briefly, the present invention is directed to mixtures comprising a monomer and a dimer, the monomer corresponding to Formula I and the dimer corresponding to Formula II



Formula (I)



Formula (II)

wherein

A_1, A_2, A_3, B_1, B_3, D_1 and D_2 are independently -CON(R)R_1 or N(R)C(O)R_2 provided, however, at least one of A_2 and A_3 is -$CONH_2$;

E_2 and E_3 are independently selected from the group consisting of -CON(R)-, -N(R)C(O)- and -NC(O)R_2-;

each R is independently H or linear or branched (C_1 - C_6) alkyl residue, optionally substituted by one to five hydroxy, alkoxy or hydroxyalkoxy groups or combinations thereof, provided, however, (i) the R substituents of at least two of A_1, B_1 and D_1 are the same as the R substituents of at least two of A_2, D_2 and E_2, and (ii) the R substituents of at least two of A_1, B_1 and D_1 are the same as the R substituents of at least two of A_3, B_3 and E_3;

each R_1 is (i) hydrogen, (ii) a linear or branched (C_1 - C_6) alkyl residue, optionally substituted by one to five hydroxy, alkoxy, hydroxyalkoxy groups or combinations thereof or by -NRC(O)R_1 or -C(O)N(R)R_1, (iii) the residue of a carbohydrate, or (iv) taken together with R and the nitrogen atom to which R and R_1 are bonded, form an alkylene chain (C_3 - C_7), said alkylene chain being optionally interrupted by -O-, -S-, -NR-, or substituted by up to five hydroxy, alkoxy or hydroxyalkoxy groups or combinations thereof;

each R_2 is (i) a linear or branched (C_1 - C_6) alkyl residue, optionally substituted by one to five hydroxy, alkoxy or hydroxyalkoxy groups, or combinations thereof or (ii) taken together with R and -NC(O)- group to which R and R_2 are bonded, form a (C_3 - C_7) cyclic residue, said cyclic residue being optionally substituted by up to five hydroxy, alkoxy or hydroxyalkoxy groups or combinations thereof; and

X is a bond or a linear or branched (C_1 - C_8) alkylene chain which is optionally substituted by up to six hydroxy groups, -C(O)NR R_1 groups, or

combinations thereof, said alkylene chain being optionally interrupted by -O-, -S-, -NR-, -N(R)C(O)- groups.

The present invention is further directed to mixtures comprising a monomer, a dimer, and at least one imaging agent other than the monomer and the dimer wherein the monomer corresponds to Formula I and the dimer corresponds to Formula II.

The present invention is further directed to a method of diagnostic imaging, the method comprising administering to an individual a contrast agent comprising a mixture of a monomer and a dimer, the monomer corresponding to Formula I and the dimer corresponding to Formula II, and carrying out an imaging procedure on such individual.

Other aspects and features of the present invention will be, in part, apparent, and, in part, pointed out hereinafter.

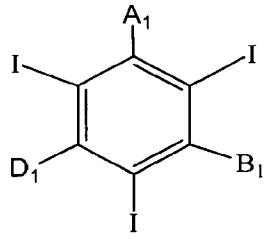
DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, it has been found that contrast media compositions corresponding to mixtures of the monomer and dimer of Formulae (I) and (II), respectively, have unexpectedly and favorably lower osmolality and viscosity values than would be predicted based solely upon the contribution of the monomer and dimer in the mixture. Without being bound to any particular theory, it appears that when a monomer and dimer have structurally similar substituents, compositions arising from such monomer-dimer mixtures have significantly favorable attractions between the monomer-dimer pairs in the mixture. These attractions appear to favor molecular aggregation and thereby reduce the effective number of particles present in solution and hence, the osmolality of the mixture.

Advantageously, X-ray contrast media comprising a mixture of a monomer and a dimer of the present invention may be prepared with both improved viscosity and osmolality characteristics. Accordingly, mixtures of the present invention preferably comprise monomer and dimer in a molar ratio of about 5:1 to about 1:1, respectively. In one embodiment, the mixture comprises the monomer and dimer in a molar ratio of about 4:1 to about 1.25:1, respectively. In one preferred embodiment, for example, the mixture comprises

the monomer and dimer in a molar ratio of about 3:1 to about 1.5:1, respectively. In another preferred embodiment, the mixture comprises the monomer and dimer in a molar ratio of about 2.5:1 to about 1.75:1, respectively. In yet another preferred embodiment, the mixture comprises the monomer and dimer in a molar ratio of about 2:1, respectively.

As previously described, contrast media of the present invention comprise a monomer corresponding to Formula I.

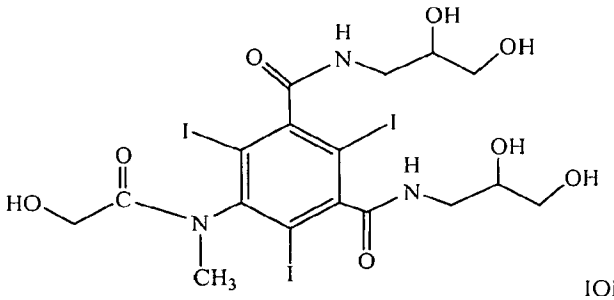


Formula (I)

wherein A_1, B_1 and D_1 are as previously defined. In one embodiment, each of A_1 and B_1 is $-C(O)N(R)R_1$ and D_1 is $-N(R)C(O)R_2$ with each R of A_1, B_1 and D_1, each R_1 of A_1 and B_1, and R_2 being independently selected from the range of substituents originally identified in connection with Formula I. For example, in this embodiment A_1 and B_1 may be -CONHR wherein each R of A_1 and B_1 is independently hydrogen, methyl, hydroxymethyl ($-CH_2OH$), ethyl, hydroxyethyl ($-CH_2CH_2OH$ or $-CH(OH)CH_3$), propyl, hydroxypropyl ($-CH_2CH_2CH_2OH$) or dihydroxypropyl ($-CH_2CH(OH)CH_2OH$); more preferably, in this embodiment, each R of A_1 and B_1 is independently hydrogen, hydroxyethyl ($-CH_2CH_2OH$ or $-CH(OH)CH_3$), hydroxypropyl ($-CH_2CH_2CH_2OH$) or dihydroxypropyl ($-CH_2CH(OH)CH_2OH$). By way of further example, in this embodiment, the R and R_2 substituents of D_1 may independently be methyl, hydroxymethyl ($-CH_2OH$), ethyl, hydroxyethyl ($-CH_2CH_2OH$ or $-CH(OH)CH_3$), propyl, hydroxypropyl ($-CH_2CH_2CH_2OH$), 1-methoxy-2-hydroxypropyl ($-CH_2CH(OH)CH_2OCH_3$), or dihydroxypropyl ($-CH_2CH(OH)CH_2OH$); more preferably, in this embodiment, the R and R_2 substituents of D_1 are preferably selected from methyl, hydroxymethyl ($-CH_2OH$), hydroxyethyl ($-CH_2CH_2OH$),and dihydroxypropyl ($-CH_2CH(OH)CH_2OH$).

In a preferred embodiment, the contrast media comprises a monomer selected from the group consisting of

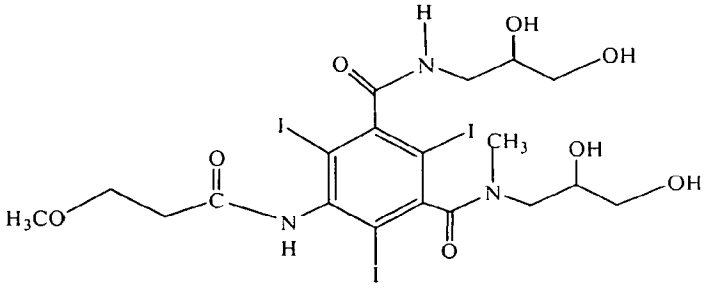
iomeprol { $C_{17}H_{22}I_3N_3O_8$; N,N'-bis(2,3-dihydroxypropyl)-5-[(hydroxyacetyl)methylamino]-2,4,6-triiodo-1,3-benzenedicarboxamide; CAS [RN] [78649-41-9]**}** ,



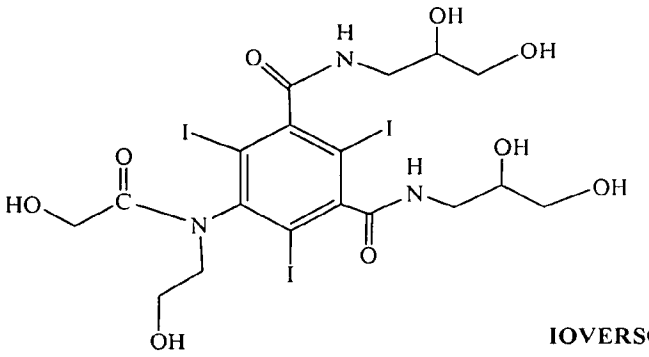
IOMEPROL

iopromide {$C_{18}H_{24}I_3N_3O_8$; N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-[(methoxyacetyl)amino]-N-methyl-1,3-benzenedicarboxamide; CAS [RN] [73334-07-3]**}** ,

IOPROMIDE

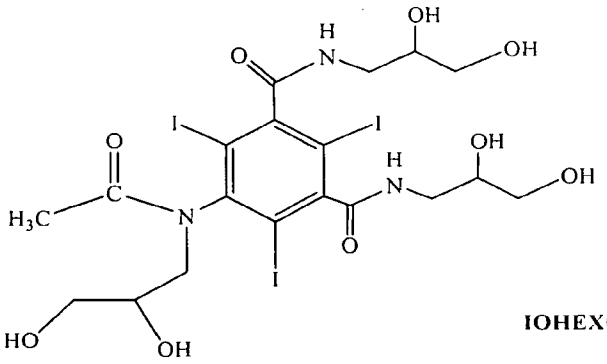


ioversol {$C_{18}H_{24}I_3N_3O_9$; N,N'-bis(2,3-dihydroxypropyl)-5-[(hydroxyacetyl)(2-hydroxyethyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide; CAS [RN] [87771-40-2]**}**,



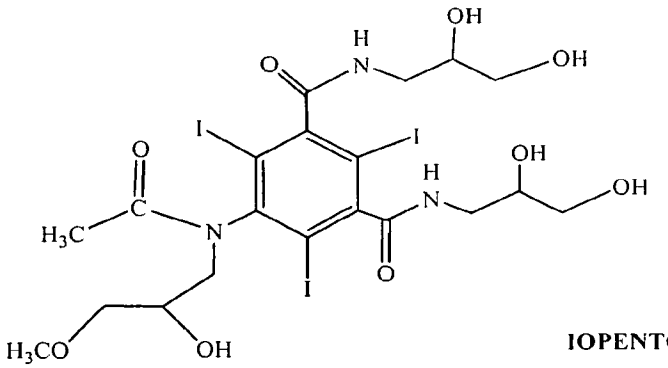
IOVERSOL

iohexol {$C_{19}H_{26}I_3N_3O_9$; 5-[acetyl(2,3-dihydroxypropyl)amino]-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide; CAS [RN] [66108-95-0]},



IOHEXOL

iopentol{$C_{20}H_{28}I_3N_3O_9$; 5-[acetyl(2-hydroxy-3-methoxypropyl) amino]-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide, CAS [RN] [89797-00-2]},

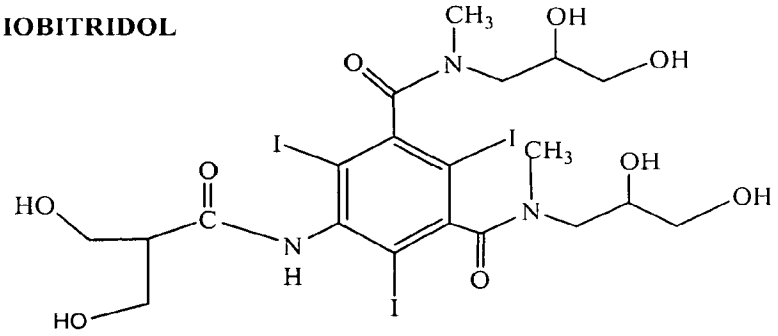


IOPENTOL

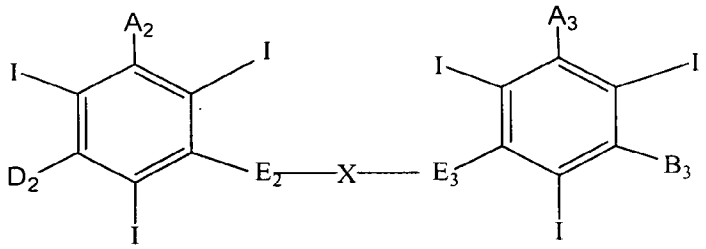
and

iobitridol{$C_{20}H_{28}I_3N_3O_9$; N,N'-bis(2,3-dihydroxypropyl)-5-[[3-hydroxy-2-(hydroxymethyl)-1-oxopropyl]amino]-2,4,6-triiodo-N,N'-dimethyl-1,3-benzenedicarboxamide; CAS [RN] [136949-58-1]}

IOBITRIDOL



Contrast media of the present invention also contain a dimer corresponding to Formula II

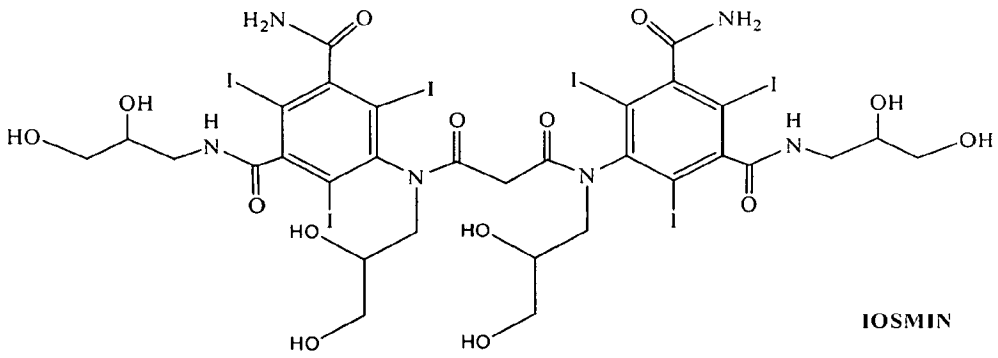


Formula (II)

wherein A_2, A_3, B_3, D_2, E_2, E_3 and X are as previously defined. In one embodiment, X is methylene (-CH_2-) or ethylene (-CH_2CH_2-), preferably methylene, and A_2, A_3, B_3, D_2, E_2 and E_3 are as originally defined in connection with Formulae I and II. In another embodiment, each of A_2 and A_3 is -C(O)NH_2, each of B_3 and D_2 is -C(O)N(R)R_1, and E_2, E_3, and X and each R and R_1 are as originally defined in connection with Formulae I and II. In another embodiment, each of A_2 and A_3 is -C(O)NH_2, each of B_3 and D_2 is -CONHR, and E_2, E_3, and X and each R are as originally defined in connection with Formulae I and II. In another embodiment, each of A_2 and A_3 is -C(O)NH_2, each of B_3 and D_2 is -C(O)NHR_1, and -E_2-X-E_3- is -N(R)C(O)CH_2C(O)N(R)- and each R and R_1 is as

originally defined in connection with Formulae I and II. In another embodiment, each of A_2 and A_3 is $-C(O)NH_2$, each of B_3 and D_2 is $-CONHR_1$, and $-E_2-X-E_3-$ is $-N(R)C(O)CH_2C(O)N(R)-$ and each R and R_1 is independently selected from hydrogen, methyl, hydroxymethyl ($-CH_2OH$), ethyl, hydroxyethyl ($-CH_2CH_2OH$ or $-CH(OH)CH_3$), propyl, hydroxypropyl ($-CH_2CH_2CH_2OH$) or dihydroxypropyl ($-CH_2CH(OH)CH_2OH$); more preferably, in this embodiment, each R and R_1 is independently hydroxyethyl, hydroxypropyl, or dihydroxypropyl. In a preferred embodiment, the contrast media comprises

iosmin {$C_{31}H_{36}I_6N_6O_{14}$; 5,5'-[(1,3-dioxo-1,3-propanediyl) bis[(2,3-dihydroxypropyl) imino]]bis[N-(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide; CAS [RN] [181872-90-2]} as the dimer:



IOSMIN

In addition, the monomer and dimer of the contrast media are selected such that (i) the R substituents of at least two of A_1, B_1 and D_1 are the same as the R substituents of at least two of A_2, D_2 and E_2, and (ii) the R substituents of at least two of A_1, B_1 and D_1 are the same as the R substituents of at least two of A_3, B_3 and E_3. For example, if the R substituents of A_1, B_1 and D_1 are identical (*e.g.*, hydrogen), then the R substituents of at least two of A_2, D_2 and E_2 are the same as the R of A_1, B_1 and D_1 (*i.e.*, hydrogen). By way of further example, if the R Substituents of A_1 and B_1 are the same (*e.g.*, hydrogen) but the R substituent of D_1 is different (*e.g.*, dihydroxypropyl), then at least one of the R substituents of A_2, D_2 and E_2 is the same as the R substituent of A_1 and B_1 (*i.e.*, hydrogen) and at least one other of the R substituents of A_2, D_2 and E_2 is the same as the R substituent of A_1, B_1 and D_1 (*i.e.*, hydrogen or dihydroxypropyl). By way of further example, if the R substituents of A_1, B_1 and D_1 are each

different (*e.g.*, hydrogen, dihydroxypropyl, and hydroxyethyl, respectively), then at least two of the R substituents of A_2, D_2 and E_2 must be different and are selected from the R substituents of A_1, B_1 and D_1 (*i.e.*, hydrogen, dihydroxypropyl, and hydroxyethyl, respectively).

Similarly, the R substituents of at least two of A_3, B_3, and E_3 are the same as A_1, B_1 and D_1 of a monomer in the mixture. For example, if the R substituents of A_1, B_1 and D_1 are identical (*e.g.*, hydrogen), then the R substituents of at least two of A_3, B_3, and E_3 are the same as the R of A_1, B_1 and D_1 (*i.e.*, hydrogen). By way of further example, if the R substituents of A_1 and B_1 are the same (*e.g.*, hydrogen) but the R substituent of D_1 is different (*e.g.*, dihydroxypropyl), then at least one of the R substituents of A_3, B_3, and E_3 is the same as the R substituent of A_1 and B_1 (*i.e.*, hydrogen) and at least one other of the R substituents of A_3, B_3, and E_3 is the same as the R substituent of A_1, B_1 and D_1 (*i.e.*, hydrogen or dihydroxypropyl). By way of further example, if the R substituents of A_1, B_1 and D_1 are each different (*e.g.*, hydrogen, dihydroxypropyl, and hydroxyethyl, respectively), then at least two of the R substituents of A_3, B_3, and E_3 must be different and are selected from the R substituents of A_1, B_1 and D_1 (*i.e.*, hydrogen, dihydroxypropyl, and hydroxyethyl, respectively).

In a particularly preferred embodiment, the contrast media comprises the dimer, iosmin, together with one or more monomers selected from the group consisting of iomeprol, ioversol, iohexol and iopentol.

Optionally, the contrast media of the present invention further contains, as an additive, an imaging agent of a class not corresponding to either of Formulae I and II. For example, the contrast media may additionally comprise X-ray contrast imaging agents not corresponding to Formula I or II. Alternatively, the contrast media may comprise other types of imaging agents and may be used for other imaging applications. Other types of imaging agents are described in H.S Thomsen, R.N. Muller and R.F. Mattrey, Editors, Trends in Contrast Media, (Berlin: Springer-Verlag, 1999); and E.M. Sevick-Muraca, et al., Near-Infrared Imaging with Fluorescent Contrast Agents, In: M.-A. Mycek and B.W. Pogue, Editors, Handbook of Biomedical Fluorescence, (New York: Marcel-Dekker, 2003, chapter 14); and are hereby incorporated by reference.

Radiological compositions may be prepared containing the above mentioned mixtures of iodinated nonionic compounds as an x-ray contrast agent together with a pharmaceutically acceptable radiological vehicle by following established methods used to manufacture such injectable formulations. Pharmaceutically acceptable radiological vehicles include those that are suitable for injection such as aqueous buffer solutions; e.g., tris(hydroxymethyl) amino methane (and its salts), phosphate, citrate, bicarbonate, etc., sterile water for injection, physiological saline, and balanced ionic solutions containing chloride and/or bicarbonate salts of normal blood plasma cations such as Ca, Na, K and Mg, and other halides, carbonates, sulphates, phosphates of Na, K, Mg, Ca. Other buffer solutions are described in Remington's Practice of Pharmacy, Eleventh Edition, for example on page 170. The vehicles may advantageously contain a small amount (*e.g.*, from about 0.01 to about 15.0 mole %) of a chelating agent such as ethylenediamine tetraacetic acid (EDTA), calcium disodium EDTA, or other pharmaceutically acceptable chelating agents such as calcium disodium DTPA-BMEA (Versetamide; Mallinckrodt Inc.). The composition further comprises a non-radiographic additives selected form excipients such as glycerol, polyethylene glycol or dextran and an anticlotting agent such as heparin or hirudin.

The concentration of the x-ray contrast agent of the present invention in the pharmaceutically acceptable vehicle, *e.g.*, water, will vary with the particular field of use. A sufficient amount is present to provide satisfactory x-ray visualization. For example, when using aqueous solutions for angiography, the concentration of iodine is generally 140-400 mg/ml and the dose is in the range of 25-300 ml. The radiological composition is administered so that the contrast agent remains in the living animal body for about 0.5 to 3 hours, although shorter and longer residence periods are acceptable as needed. Thus, for vascular visualization, the mixture disclosed herein and analogous mixtures may be formulated conveniently in vials, ampules or prefilled syringes containing 10 to 500 ml. of an aqueous solution.

The diagnostic compositions of the invention are used in the conventional manner. The compositions may be administered to a patient, typically a warm-blooded animal, either systemically or locally to the organ or tissue to be imaged,

optimally using a power injector when appropriate, and the patient then subjected to the imaging procedure. For example, in the case of selective coronary arteriography, an amount of the radiological composition, sufficient to provide adequate visualization, is injected into the coronary system and the system is scanned with a suitable device such as a fluoroscope. The agent may be used in various other radiographic procedures e.g., in cardiography, coronary arteriography, aortography, cerebral and peripheral angiography, orthography, intravenous pyelography and urography.

X-ray contrast Imaging Procedures are found in Albert A. Moss, M. D., Gordon Gamsu, M. D., and Harry K. Genant, M. D., Computed Tomography of the Body, (Philadelphia, PA: W. B. Saunders Company, 1992) and M. Sovak, Editor, Radiocontrast Agents, (Berlin: Springer-Verlag, 1984).

EXAMPLES

Example 1

A novel mixed XRCM formulation is to be generated starting with enough dimer, iosmin, to give an iodine concentration of 280 mg I/ml to which is added ioversol to raise the iodine concentration to 320 mg I/ml. After addition of buffer and stabilizer, the formulation will be autoclaved following the standard procedure. The values of osmolality and viscosity will be measured and compared with the expected or calculated value, i.e. calculated based on the contribution from the quantities of iosmin and ioversol present in the 320 mg I/ml formulation. It is expected that viscosity of this mixed formulation will be lower than the theoretical value. If the osmolality of this mixed formulation is below 300 mOsm/kg, other appropriate additives including ioversol could be added to make it iso-osmolal with blood.

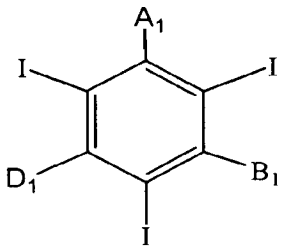
Example 2

Three sets of XRCM formulations will be generated at 320 mgI/ml concentration (with the buffer and stabilizer) as follows; (i) one with iosmin, (ii) the other with ioversol and (iii) the third, for example, as a 50:50 mixture of iosmin and ioversol (based on iodine content). The values of osmolality and viscosity will be measured and compared with the theoretical, i.e. calculated, based on the contribution from the quantity of iosmin and ioversol present. It is expected that the viscosity of the third formulation will be lower than the average of the first two formulations.

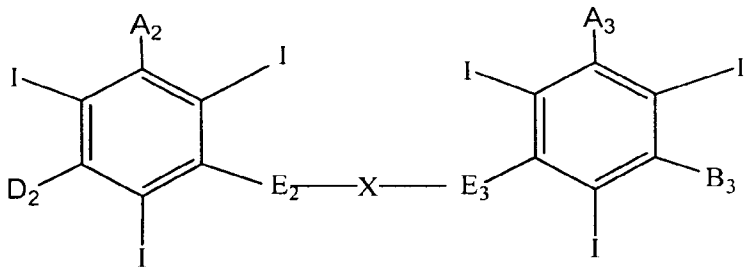
CLAIMS

What is claimed is:

1. An injectable radiological composition for x-ray visualization during radiological examinations, the composition comprising a pharmaceutically acceptable vehicle and a mixture of a monomer and a dimer, the monomer corresponding to Formula I and the dimer corresponding to Formula II



Formula (I)



Formula (II)

wherein

A_1, A_2, A_3, B_1, B_3, D_1 and D_2 are independently -CON(R)R_1 or -N(R)C(O)R_2 provided, however, at least one of A_2 and A_3 is -$CONH_2$;

E_2 and E_3 are independently selected from the group consisting of -CON(R)-, -N(R)C(O)- and -NC(O)R_2-;

each R is independently H or linear or branched (C_1 - C_6) alkyl residue, optionally substituted by one to five hydroxy, alkoxy or hydroxyalkoxy groups or combinations thereof, provided, however, (i) the R substituents of at least two of A_1, B_1 and D_1 are the same as the R substituents of at least two of A_2, D_2 and E_2, and (ii) the R substituents of at least two of A_1, B_1 and D_1 are the same as the R substituents of at least two of A_3, B_3 and E_3;

each R_1 is (i) hydrogen, (ii) a linear or branched (C_1 - C_6) alkyl residue, optionally substituted by one to five hydroxy, alkoxy, hydroxyalkoxy groups or combinations thereof or by -NRC(O)R_1 or -C(O)N(R)R_1, (iii) the residue of a

carbohydrate, or (iv) taken together with R and the nitrogen atom to which R and R_1 are bonded, form an alkylene chain (C_3 - C_7), said alkylene chain being optionally interrupted by -O-, -S-, -NR-, or substituted by up to five hydroxy, alkoxy or hydroxyalkoxy groups or combinations thereof;

each R_2 is (i) a linear or branched (C_1 - C_6) alkyl residue, optionally substituted by one to five hydroxy, alkoxy or hydroxyalkoxy groups, or combinations thereof or (ii) taken together with R and -NC(O)- group to which R and R_2 are bonded, form a (C_3 - C_7) cyclic residue, said cyclic residue being optionally substituted by up to five hydroxy, alkoxy or hydroxyalkoxy groups or combinations thereof; and

X is a bond or a linear or branched (C_1 - C_8) alkylene chain which is optionally substituted by up to six hydroxy groups, -C(O)NR R_1 groups, or combinations thereof, said alkylene chain being optionally interrupted by -O-, -S-, -NR-, -N(R)C(O)- groups.

2. The composition of claim 1 wherein A_2 and A_3 are each -C(O)NH_2.

3. The composition of claim 1 or 2 wherein X is methylene.

4. The composition of claim 1, 2 or 3 wherein A_1 and B_1 are -C(O)N(R)R_1, and each R and R_1 of A_1 and B_1 are as defined in claim 1.

5. The composition of claim 4 wherein D_1 is -N(R)C(O)R_2, and R and R_2 are as defined in claim 1.

6. The composition of claim 1, 2 or 3 wherein A_1 and B_1 are -CONHR wherein each R of A_1 and B_1 is independently hydrogen, methyl, hydroxymethyl, ethyl, hydroxyethyl, propyl, hydroxypropyl, or dihydroxypropyl.

7. The composition of claim 6 wherein D_1 is -N(R)C(O)R_2, and R and R_2 are as defined in claim 1.

8. The composition of claim 1, 2 or 3 wherein A_1 and B_1 are -CONHR wherein each R of A_1 and B_1 is independently hydrogen, hydroxyethyl hydroxypropyl, or dihydroxypropyl.

9. The composition of claim 8 wherein D_1 is $-N(R)C(O)R_2$, and R and R_2 are as defined in claim 1.

10. The composition of claim 9 wherein A_1 and B_1 are -CONHR wherein each R of A_1 and B_1 is independently hydrogen, methyl, hydroxymethyl, ethyl, hydroxyethyl, propyl, hydroxypropyl, or dihydroxypropyl

11. The composition of claim 1, 2 or 3 wherein D_1 is $-N(R)C(O)R_2$, and the R and R_2 substituents of D_1 are independently methyl, hydroxymethyl, ethyl, hydroxyethyl, propyl, hydroxypropyl, 1-methoxy-2-hydroxypropyl, or dihydroxypropyl.

12. The composition of claim 11 wherein A_1 and B_1 are -CONHR wherein each R of A_1 and B_1 is independently hydrogen, methyl, hydroxymethyl, ethyl, hydroxyethyl, propyl, hydroxypropyl, or dihydroxypropyl

13. The composition of claim 1, 2 or 3 wherein D_1 is $-N(R)C(O)R_2$, and the R and R_2 substituents of D_1 are independently methyl, hydroxyethyl, or dihydroxypropyl.

14. The composition of claim 13 wherein A_1 and B_1 are -CONHR wherein each R of A_1 and B_1 is independently hydrogen, methyl, hydroxymethyl, ethyl, hydroxyethyl, propyl, hydroxypropyl, or dihydroxypropyl

15. The composition of any of claims 3-14 wherein A_2 and A_3 are $-C(O)NH_2$.

16. The composition of claim 1 or 15 wherein the R_1 substituent of at least one of A_1, B_1 and D_1 is hydrogen.

17. The composition of any of claims 1, 15, and 16 wherein the R_1 substituents of at least two of A_1, B_1 and D_1 are hydrogen.

18. The composition of any of claims 1, and 15-17 wherein one of A_1, B_1 and D_1 is $-N(R)C(O)R_2$ and R and R_2 of D_1 is as defined in claim 1.

19. The composition of claim 1 wherein the monomer is selected from the group consisting of iomeprol, iopromide, ioversol, iohexol, iopentol, and iobitridol.

20. The composition of any of claims 1-19 wherein the dimer is iosmin.

21. The composition of any of claims 1-20 wherein the composition further comprises a non-radiographic additives selected form excipients, stabilizers, control agents for dissolution, physiologically tolerable water-soluble mineral salts, wherein said mineral salts are halides, carbonates, bicarbonates, sulphates, phosphates of Na, K, Mg, Ca and an anticlotting agent which is heparin or hirudin.

22. The composition of claim 21 wherein said excipient is glycerol, polyethylene glycol or dextran.

23. The composition of claim 21 wherein said stabilizer is tromethamol, H_4EDTA, $EDTACaNa_2$, or sodium phosphate.

24. The composition of any of claims 1-23 wherein the composition comprises a contrast agent other than the monomer and the dimer.

25. A method of diagnostic imaging, the method comprising administering to an individual a composition of any of claims 1-24, and carrying out an imaging procedure on such individual.

ABSTRACT

The present invention generally relates to nonionic x-ray contrast media formulations, radiological compositions containing such agents and methods for x-ray visualization utilizing such compositions. The invention especially relates to injectable radiological compositions for x-ray visualization comprising a pharmaceutically acceptable vehicle and a mixture of a monomer, being a triiodo-substituted nucleus, and a dimer, being two linked triiodo-substituted nuclei, such that the mixture demonstrates favorable biological properties.